UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/612,192	07/02/2003	Ranajit Pal	00711CIP	4134

35467 7590 11/20/2006

BIOMERIEUX, INC.
PATENT DEPARTMENT
100 RODOLPHE STREET
DURHAM, NC 27712

EXAMINER	
PENG, BO	

ART UNIT	PAPER NUMBER
1648	

DATE MAILED: 11/20/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/612,192	PAL ET AL.	
	Examiner	Art Unit	
	Bo Peng	1648	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *28 August 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *8-14 and 16-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-7 and 15* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *12/3/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The examiner of your application in the Patent and Trademark Office has been changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Bo Peng, Art Unit 1648.

Restriction election

2. The Office acknowledges the receipt of Applicant's restriction election, filed on August 28, 2006. Applicant elects, with traverse, Group I, Claims 1-7 and 15. Because Applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)). This restriction is made FINAL.

3. Accordingly, Claims 1-7 and 15 are pending. Claims 8-14 and 16-20 are withdrawn from consideration as nonelected inventions. Claims 1-7 and 15 are examined in this Office action.

Claim Rejections - 35 USC § 101 Utility

4. 35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

5. Claim 15 is rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a credible asserted utility or a well-established utility.

6. Claim 15 is directed to a vaccine comprising an immunogenically effective amount of a

complex of gp120 covalently bonded to a fragment of CD4 or an equivalent thereof in a pharmaceutically acceptable medium.

7. The term "vaccine" by definition implies a preparation intended for active immunological prophylaxis; e. g., preparations of killed microbes of virulent strains or living microbes of attenuated (variant or mutant) strains or microbial, fungal, plant, protozoa, or metazoan derivatives or products. Although just about any protein when inoculated can cause an immune reaction, the prophylactic nature of this reaction is not guaranteed and has to be experimentally determined. Prophylaxis is defined as the prevention of disease or of a process that can lead to disease. This is achieved by use of an antigenic (immunogenic) agent to actively stimulate the immunological mechanism, or the administration of chemicals or drugs to members of a community to reduce the number of carriers of a disease and to prevent others from contracting the disease.

8. Up to now, HIV vaccines have not established either a credible asserted utility or a well-established utility because none of HIV vaccine is effective for the intended purpose due to the well-known difficulties inherent to development of HIV vaccines. Some of those problems are outlined here:

1) the extensive genomic diversity associated with the HIV retrovirus, due in large part to error prone reverse transcription of its single-stranded RNA genome,

2) the existence of latent forms of the virus,

3) the ability of the virus to "immune escape" from natural and adoptive immunity against the virus,

4) the modes of viral transmission, including both cell-to-cell and free virus transmission,

5) the complexity and variation of the elaboration of the disease and,

6) the property of some portions of HIV proteins or peptides to actually cause immunosuppression or other detrimental consequences.

9. The existence of these obstacles prevents one of ordinary skill in the art from recognizing that current HIV vaccines have either a credible asserted utility or a well-established utility. "The inability to solve fundamental scientific questions is the root cause for why a successful vaccine is not currently with our grasp" (Desrosiers RC. Nature Medicine Vol. 10 (2004), pp. 221-223). To date, several clinical trials have been conducted but in every situation, the immunogen failed to induce protective immunity, failed to control viremia, and failed to protect individuals at a high risk from infection. Moreover, no experimental vaccine candidates so far have been proven to be effective to protect monkeys from SIV infection in animal models.

10. The existence of these obstacles also prevents one of ordinary skill in the art from accepting any vaccine regimen on its face. In order to provide proof of utility with regard to drugs and their uses, either clinical or *in vivo* or *in vitro* data, or a combination of these can be used. However, the data must be such as to convince one of ordinary skill in the art that the proposed utility is sufficiently established. See in re Irons, 340 F. 2d 924,144 USPQ 351 (CCPA 1965), Ex parte Krepelka, 231 USPQ 746 (PTO Bd. Pat. App & Inter.1986) and Ex pane Chwang, 231 USPQ 751 (PTO Bd. Pat. App & Inter. 1986). In the instant case, the *in vitro* data presented in the specification is insufficient to convince one of ordinary skill in the art that claim vaccine can be effective for its intended use, that is the production of protective immunity in human to prevent disease (HIV infection). Thus, considering the insufficient scientific data provided in the specification, the complex state and nature of the art of HIV vaccine

development, the claimed vaccine has not established either a credible asserted utility or a well-established utility.

Claim Rejections - 35 USC § 112, first paragraph

11. The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

12. Claim 15 is further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

"[T]o be enabling, the specification of a patent must teach those skilled in the art how to make and use the full scope of the claimed invention without 'undue experimentation.'" Genentech Inc. v. Novo Nordisk 108 F.3d 1361, 1365, 42 USPQ2d 1001, 1004 (Fed. Cir. 1997); In re Wright 999 F.2d 1557, 1561, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993); See also Amgen Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir. 1991); In re Fisher 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). Further, in In re Wands 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988) the court stated:

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized by the board in Ex parte Forman [230 USPQ 546, 547 (BdPatAppInt 1986)]. They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5)

the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed. Cir. 1993).

13. As discussed above, the state of the art has shown that development of vaccine against HIV infection is unpredictable. The less is known about the art of the invention in the art, the more details would need in the specification as to how to use the invention in order for a person of skill in the art to be enabled to use the claimed invention. The disclosure, however, fails to provide any working embodiments to show that claimed vaccine regiment gp120-CD4 complex would elicit a protective immunity against HIV infection, and what "an immunogenically effective amount of" the complex of gp120-CD4 or an equivalent thereof is to induce protective immunity. The specification shows the antibodies generated using gp120-CD4 complex can neutralize lab-adapted strains HIV_{IIIB} and $HIV\text{-}1_{MN}$ in an *in vitro* assay. However, the specification lacks adequate teachings to show that such neutralizing antibody can also neutralize primary HIV strains. Cohen (Science 262:980-981, cited in IDS) has reported that even though antibodies may protect against this lab-adapted virus they may be ineffective against a real-world strain of HIV. A more realistic test is to use HIV that has been freshly harvested from patients, because these "primary field isolates" are believed to be much closer to the type of HIV that would infect a vaccinated person. "While most of the samples beat back lab-adapted strains of

HIV, not one could neutralize a field isolate. The obvious implication is that the immunogens used to date don't induce the breadth of response needed to neutralize primary isolates." (Cohen, page 980).

14. Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in Ex parte Forman, 230 USPQ 546 (BPAI 1986) and reiterated by the Court of Appeals in *In re Wands*, 8 USPQ 2d 1400 at 1404 (CAFC 1988). In the instant specification, 1) there are no working examples which suggest the desired results of a vaccine which would raise neutralizing antibodies in humans and protect against HIV infection, 2) the nature of the invention involved the complex and incompletely understood area of immune responses important in HIV disease, and 3) the state of the prior art shows that prior vaccines designed to produce neutralizing antibody responses against HIV infection have been largely ineffective for the intended purpose. Even though the skill in the art is high, given the lack of guidance and working examples to show the neutralizing antibodies elicited using gp120-CD4 and an equivalent thereof is capable to neutralize primary HIV in vivo, the quantity of experimentation *in vitro* and *in vivo* necessary to practice the claimed invention is undue. Therefore, considering the broad scope of the claim, the complex state and nature of the art, unpredictability from the prior art, Applicant has not provided sufficient information to enable the full breath of the claimed invention without undue experimentation.

Claim Rejections - 35 USC § 112, first paragraph-Scope of Enablement

15. Claims 1-7 are rejected under 35 U.S.C. 112, first paragraph, because the specification,

while being enabling for an immunogenic complex comprising gp120 bonded to a fragment of CD4, does not reasonably provide enablement for an immunogenic complex comprising gp120 bonded to an CD4 equivalent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

16. Claims 1-7 are directed to an immunogenic complex comprising gp120 covalently bonded to a fragment of CD4 or an equivalent thereof. In the specification, "CD4 equivalent molecules" is defined as "include any molecule that mimics CD4 in conformation and/or induces a conformational change on HIV-1 gp120 that is similar to that induced by CD4." (paragraph [0033]. Thus, neither the instant claims nor specification provides specific structure description about "an CD4 equivalent thereof". Moreover, the only function limitation for such fusion molecules with no defined structures is "wherein cryptic epitopes are revealed" (Claim 3). In the specification, however, no specific "cryptic epitopes", such as the minimal structures and correlation between structure and function, are identified or described in the specification. Since the cryptic epitopes are undefined, the function limitation to reveal such cryptic epitopes is not defined. As a result, there is no either structure or function limitation to "an immunogenic complex" comprising gp120 covalently bonded to an equivalent of CD4 fragment of Claim 1-7.

17. Because of the lack of structural specificity of the claimed fusion proteins and "cryptic epitopes" in claims 1-7, it is impossible for one skilled in the art to know how to make the instant fusion molecules with no defined structures and functions. Although applicant discloses a fusion peptide of gp120-CD4 in the specification, Applicant has not disclosed any other fusion molecules that equivalent to gp120-CD4 to support all undefined fusion molecules. One skilled

in the art would have to do an **undue** amount of experimentation to make and test all fusion molecules to see if such molecules are an equivalent to CD4 to reveal unknown cryptic epitopes of gp120. Therefore, the instant invention, based on the evidence as a whole, in light of the factors articulated by the court in *In re Wands*, lacks an enabling disclosure.

Claim Rejections - 35 USC § 112, first paragraph-Written Description

18. Claims 1-7 are further rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

19. As discussed above, since there is no limitation to "an equivalent thereof", the scope of "an immunogenic complex and vaccine comprising gp120 covalently bonded to a fragment of CD4 or an equivalent thereof " encompasses any fusion polypeptides with no defined structures. Although applicant discloses a fusion peptide of gp120-CD4 in the specification, Applicant has not disclosed sufficient species of fusion molecules that equivalent to gp120-CD4, such as definite structural features, to support the broadly claimed genus of all undefined gp120-CD4 equivalent. Consequently, while the skilled artisan would reasonably conclude Applicant was in possession of the gp120-CD4, there is no indication that Applicant was in possession of all undefined immunogenic complex that equivalent to gp120-CD4 as broadly claimed.

Double Patenting

20. Claims 1-7 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 1 of US 5,843,454, and claim1 of US 5,518,723. Although the conflicting claims are not identical, they are not patentably distinct from each other because three sets of claims are drawn to same products.

21. Claims 1-7 are drawn to an immunogenic complex comprising gp120 covalently bonded to a fragment of CD4 or an equivalent thereof (Claim 1), wherein said fragment of CD4 comprises the first and second domains of CD4, wherein cryptic epitopes are revealed, wherein said gp120 is covalently cross-linked to said fragment of CD4. A composition comprising the immunogenic complex of claim 1 (Claim 5), wherein the composition further comprises an adjuvant composed of aluminum phosphate gel, and a pharmaceutically acceptable carrier.

22. Claim 1 of US 5,518,723 is drawn to an immunogenic complex comprising gp120 covalently bonded to CD4 such that cryptic epitopes are revealed.

23. Claim 1 of US 5,843,454 is drawn to a composition comprising: an immunogenic complex comprising gp120 covalently bonded to CD4; and an adjuvant composed of aluminum phosphate gel.

24. Since the gp120-CD4 complex of both 5,518,723 and 5,843,454 meets the structure and function limitations of "an immunogenic complex comprising gp120 covalently bonded to a fragment of CD4 or an equivalent thereof", the subject maters of three sets of claims are not patentable distinct from each other. Therefore, the instant claims 1-7 are anticipated by 5,518,723 and 5,843,454.

Remarks

25. No claim is allowed.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bo Peng, Ph.D. whose telephone number is 571-272-5542. The examiner can normally be reached on M-F, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, Ph.D., can be reached on 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Bo Peng, Ph.D.

BRUCE R. CAMPELL, PH.D
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600